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Immature granulocyte and other markers in prediction of the short-term and long-term prognosis of patients with acute ischemic stroke

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Abstract

Background & Objectives: To evaluate immature granulocytes, a new inflammatory biomarker, and other markers in short- and long-term prognosis in patients with acute ischemic stroke (AIS). *Methods:* Laboratory information system data from a tertiary hospital in Turkiye were used in this retrospective study. Of the 327 patients with the diagnosis of AIS, 275 recovered, and 52 died. It was determined that 31 of these 275 patients, who were followed up retrospectively, died within 12 months after discharge. Routinely measured immature granulocyte (IG), other hemogram parameters in the Sysmex XN 1000 (XN-1000-Hematology-Analyzer-Sysmex Corporation, Japan), and demographic data were statistically compared in both groups. We tried to estimate the short- and long-term mortality from the blood samples of these patients at their first admission to the hospital. *Results:* Of the patients included in the study, 150 (45.9%) were female, and 177 (54.1%) were male. National Institutes Of Health Stroke Scale (NIHSS) (AUC=960), length of stay (AUC=791), red blood cell distribution width – standard deviation (RDW-CV) (AUC=728), and IG (AUC=712) were the most effective parameters in predicting short-term mortality, while age (AUC=764) in predicting long-term mortality was the most effective parameters.
Conclusion: IG, together with NIHSS and length of stay, shows moderate and high predictive properties in prognosticating short-term mortality but is ineffective in prognosticating long-term mortality. Age was found to be the most predictive marker for long-term mortality.

Keywords: Acute ischemic stroke, inflammation, immature granulocyte, prognosis, mortality

INTRODUCTION

Stroke is a serious neurological disease with a high rate of long-term disability and mortality. It is well-known that ischemic stroke is the most common seen in 90% of all strokes. Stroke has an annual prevalence of around 6/1000, and ischemic stroke is an important cause of death in many communities, along with cardiovascular diseases. Understanding the mechanism of development of the disease is important to predict mortality. Inflammation is an important variable for explaining the pathophysiology of acute ischemic stroke.[1,2] The levels of inflammatory mediators have been measured in normal brain tissue. Proinflammatory cytokines are released from ischemic tissue, thus continuously releasing immune cells. The relationship between NLR (neutrophil-lymphocyte ratio), LMR (lymphocyte-monocyte ratio), and PLR (platelet-lymphocyte ratio) as a marker of systemic inflammation and poor prognostic in cases with acute ischemic stroke (AIS) has been documented in recent studies.[3]

Immature granulocyte (IG) is an inflammatory parameter easily obtained from an automatic blood cell analyzer. Recent studies have shown that IG is useful in predicting sepsis, septic shock, acute appendicitis, and pancreatitis complications and mortality.[4] Whereas, only one study observes the relationship between IG and the 30-day mortality of AIS patients.[5] However, we could not find an article in the literature investigating the connection between immature granulocyte and long-time period mortality in patients with AIS. Therefore, we aimed to investigate the function of IG and other labels in predicting short- and long-time mortality in patients with AIS.

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METHODS

This retrospective study was conducted in a tertiary hospital in Turkiye. The computing management system of the hospital between January 2020 and August 2021, and 327 patients admitted to the emergency department with the diagnosis of acute ischemic stroke and hospitalized in the neurology clinic was searched to collect data in this study. While 275 of these patients constituted the group that recovered after treatment, 52 died despite the treatment. These 275 patients who recovered were followed up for 12 months. In this time interval, 31 of these patients had died, and 244 were living. The following patient groups were excluded from the study: Under the age of eighteen, pregnant women, trauma patients, and patients without laboratory data. Routinely measured IG, other hemogram parameters in the Sysmex XN 1000 (XN-1000-Hematology-Analyzer-Sysmex Corporation, Japan), and demographic data were statistically compared in both groups. We attempted to estimate the short and long-term mortality of the patients.

Statistical analysis

The "Statistical Package for Social Sciences 18.0 for Windows" (SPSS Inc., Chicago, USA) program was used for statistical analysis of the data. Descriptive statistics of the obtained data were given as numbers and % for categorical variables and as median (25 Percentile, 75 Percentile) for numerical variables. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. The Mann-Whitney U test was used to compare the data between the deceased and surviving groups since the data did not fit the normal distribution. Groups with nominal distribution such as gender, diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), atrial fibrillation (AF), coronary artery disease (CAD), previous stroke, Glasgow Coma Score (GCS), National Institutes Of Health Stroke Scale (NIHSS), acetylsalicylic acid (ASA), oral anticoagulant (OA), antihypertensive (AH), statin use, large vessel involvement, small vessel involvement, and cardioembolic event were compared with the chi-square test. Receiver operating characteristic (ROC) analysis was performed and the Youden index was used to determine the Area Under the Curve (AUC), cut-off, sensitivity, and specificity values. Univariate and multivariate Cox regression analyses were performed for hospital survival analysis. Univariate and multivariate logistic regression analysis was performed for long-term survival analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 327 AIS patients who met the inclusion criteria were included in the study. Of these patients, 150 (45.9%) were female and 177 (54.1%) were male. The median age of the patients was 75 (65;81). As for co-morbidity, 86 (26.4%) patients had DM, 211 (64.6%) had HT, 88 (27.0%) had HL, 77 (23.6%) people had AF, 93 (28.5%) people had CAD, 40 (12.3%) patients had a previous stroke, 74 (22.7%) patients used ASA, 42 (12.9%) patients used OA, 180 (55.2%) patients used AH, 36 (11.0%) patients used statins, 75 (23.0%) patients had large vessel occlusion, 77 (23.6%) patients had cardioembolism, 176 (54.0%) patients had small vessel occlusion. When we look at the medians of other data, GCS 15(13;15), NIHSS 4(3;7), WBC 8.4(6.6;10.2), RDW-SD 43.4(40.4;46.6), RDW-CV 13.5(13.0;14.6), NEUT # 5.45(4.19;7.81), IG# 0.03(0.02;0.05), IG 0.4%(0.3;0.5) and NLR 3.23(2.07;5.58) (Table 1). For short-term mortality (Table 1), 52 people were deceased group and 275 were the survivor group.

In estimating long-term mortality, the patients' demographic, clinical, and hemogram data (Table 2) show that 31 people constitute the deceased group and 244 are the survivors.

In the ROC analysis, IG count and IG% showed moderate predictive properties (cut off: 0.045, AUC = 0.712)(cut off: 0.35, AUC = 0.682) (Table 5, Figure 1) for short-term mortality.

Age was the most predictive marker for long-term mortality (cut off: 83.5, AUC = 0.764) (Table 6, Figure 2).

In univariate and multivariate cox regression analyses, NIHSS and IG% were independent markers for short-term mortality (Table 7).

In univariate and multivariate logistic regression analyses, NIHSS and age were independent predictors of long-term mortality (Table 8).

DISCUSSION

One of the most important results of our study is that IG is an inexpensive, accessible, and important prognostic marker for predicting short-term mortality in cases with AIS. This study also observed that NIHSS, length of hospital stay,

Table 1: Comparison of demographic, clinical and hemogram data of short-term mortality of patients with AIS

	Deceased (52)	Survival (275)	p
Age (year)	78(74;84)	72(63;80)	<0.001
Male Gender n(%)	24(46.2)	153(55.6)	0.208
Clinical History			
DM	14(27.5)	72(26.2)	0.850
HT	35(68.6)	176(64.0)	0.525
HL	2(3.9)	86(31.3)	<0.001
AF	16(31.4)	61(22.2)	0.156
CAD	17(33.3)	76(27.6)	0.408
Prior Stroke	3(5.9)	37(13.5)	0.130
GCS	11(8;12)	15(14;15)	<0.001
NIHSS	13(10;18)	3(2;5)	<0.001
Pre Stroke Medications			
ASA	3(5.9)	71(25.8)	0.003
OA	11(21.6)	31(11.3)	0.044
AH	27(52.9)	153(55.6)	0.722
Statin	1(2.0)	35(12.7)	0.044
Subgroups According to Etiology, n (%)			
Large Vessel	35(68.6)	40(14.5)	<0.001
Cardioembolic	14(27.5)	63(22.9)	0.483
Small Vessel	2(3.9)	174(63.3)	<0.001
Length Of Stay	16.0(8.3;34.5)	6(5;8)	<0.001
Laboratory Features			
WBC ($x10^9$/L)	10.3(7.9;13)	8.2(6.54;10.02)	<0.001
RDW-SD (fL)	46.9(43.1;50.5))	42.8(40.2;46.0)	<0.001
RDW-CV (%)	14.65(13.6;17.4)	13.5(12.9;14.4)	<0.001
NEUT# ($x10^9$/L)	7.83(5.4;10.9)	5.22(4.05;7.2)	<0.001
LYMPH# ($x10^9$/L)	1.21(0.73;2.26)	1.7(1.18;2.35)	0.006
NEUT%	77.1(67.0;84.3)	66.6(59.2;75.7)	<0.001
LYMPH%	14.85(7.6;22.7)	22.5(15.2;29.3)	<0.001
IG# ($x10^9$/L)	0.05(0.03;0.09)	0.03(0.02;0.05)	<0.001
IG%	0.5(0.4;0.8)	0.4(0.3;0.5)	<0.001
NLR	5.1(2.9;11.0)	2.96(2.0;4.9)	<0.001
SII	1083(541;2558)	707(417;1188)	<0.001

Abbrevations: DM, diabetes mellitus; HT, hypertension; HL, hyperlipidemia; AF, atrial fibrillation; CAD, coronary artery disease; GCS, Glasgow Coma Score; NIHSS, National Institutes Of Health Stroke Scale; ASA, acetylsalicylic acid; OA, oral anticoagulant; AH, antihypertensive; WBC, white blood cell; RDW-CV, red blood cell distribution width – coefficient of variation; RDW-SD, red blood cell distribution width – standard deviation; NEUT#, neutrophil count; NEUT%, neutrophil percentage; LYMPH#, lymphocyte count; LYMPH%, lymphocyte percentage; IG#, immature granulocyte count; IG%, immature granulocyte percentage; NLR, neutrophil-lymphocyte ratio; SII, systemic immune-inflammation index

Table 2: Comparison of demographic, clinical and hemogram data of patients with AIS who died and survived long term

	Deceased (31)	Survival (244)	p
Age	84(72;88)	72(62;80)	<0.001
Male Gender n(%)	17(54.8)	136(55.7)	0.924
Clinical History			
DM	7(22.6)	65(26.6)	0.628
HT	21(67.7)	155(63.5)	0.645
HL	7(22.6)	79(32.4)	0.268
AF	10(32.3)	51(20.9)	0.152
CAD	11(35.5)	65(26.6)	0.300
Prior Stroke	4(12.9)	33(13.5)	0.924
GCS	14(12;15)	15(14;15)	0.004
NIHSS	5(3; 8)	3(2;5)	0.004
Pre-stroke Medications			
ASA	8(25.8)	63(25.8)	0.999
OA	4(12.9)	27(11.1)	0.761
AH	18(58.1)	135(55.3)	0.773
Statin	2(6.5)	33(13.5)	0.266
Subgroups According to Etiology, n (%)			
Large Vessel	8(25.8)	32(13.1)	0.059
Cardioembolic	9(29.0)	54(22.1)	0.389
Small Vessel	15(48.4)	159(65.2)	0.068
Length Of Stay	7(6;12)	6(5;8)	0.010
Subgroups According to Etiology, n (%)			
WBC($x10^9$/L)	7.4(6.7;9.9)	8.2(6.5;10.02)	0.435
RDW-SD	44(42;49.2)	42.6(40.2;45.5)	0.016
RDW-CV	14.1(13.2;15.1)	13.4(12.9;14.2)	0.009
EO#($x10^9$/L)	0.05(0.01;00.9)	0.11(0.04;0.18)	<0.001
LYMPH#($x10^9$/L)	1.32 (1.02;2.00)	1.72(1.26;2.40)	0.004
NEUT%	70.6(64.9;79.8)	66.0(58.5;74.7)	0.021
LYMPH%	18.8(11.5;25.4)	22.9(16.1;29.6)	0.038
IG#($x10^9$/L)	0.03(0.02;0.04)	0.03(0.02;0.05)	0.527
IG%	0.4(0.3;0.5)	0.4(0.3;0.5)	0.989
NLR	3.8(2.6;6.6)	2.9(1.9;4.7)	0.029
PLR	166(102;243)	130(91;171)	0.012

Abbrevations: DM, diabetes mellitus; HT, hypertension; HL, hyperlipidemia; AF, atrial fibrillation; CAD, coronary artery disease; GCS, Glasgow Coma Score; NIHSS, National Institutes Of Health Stroke Scale; ASA, acetylsalicylic acid; OA, oral anticoagulant; AH, antihypertensive; WBC, white blood cell, RDW-CV, red blood cell distribution width – coefficient of variation; RDW-SD, red blood cell distribution width – standard deviation; EO#, eosinophil count; NEUT%, neutrophil percentage; LYMPH#, lymphocyte count; LYMPH%, lymphocyte percentage; IG#, immature granulocyte count; IG%, immature granulocyte percentage; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio

Table 5: ROC analysis values of some hematological and demographic data in evaluating short-term mortality in AIS patients

	Cut-off	AUC	95%CI	p	%Sensivity	%Spesifity
WBC(x10^9/L)	10.5	0.669	0.58-0.72	<0.001	51	82
RDW-SD (fL)	44.5	0.705	0.62-0.79	<0.001	73	66
RDW-CV%	14.25	0.728	0.65-0.81	<0.001	63	75
NEUT#(x10^9/L)	7.09	0.700	0.62-0.78	<0.001	59	74
NEUT%	73.25	0.708	0.63-0.79	<0.001	63	71
IG#(x10^9/L)	0.045	0.712	0.63-0.80	<0.001	63	74
IG%	0.35	0.682	0.60-0.77	<0.001	84	46
NLR	4.18	0.710	0.63-0.79	<0.001	65	70
Age	73.5	0.651	0.58-0.72	<0.001	78	53
Length Of Stay	11.5	0.791	0.71-0.88	<0.001	63	89
NIHSS	6.5	0.960	0.94-0.98	<0.001	96	85

Abbrevations: WBC, white blood cell; RDW-CV, red blood cell distribution width – coefficient of variation; RDW-SD, red blood cell distribution width – standard deviation; NEUT#, neutrophil count; NEUT%, neutrophil percentage; IG#, immature granulocyte count; IG%, immature granulocyte percentage; NLR, neutrophil-lymphocyte ratio; NIHSS, National Institutes Of Health Stroke Scale

RDW, and NLR were effective predictors of short-term mortality. Age, length of stay, RDW, and eosinophil count were effective predictors of long-term mortality. However, the number of IG was not effective for estimating long-term mortality. In several studies, IG is an important biomarker in predicting short-term mortality in patient groups.[6,7] However, as far as we know, there is no study todate in the literature on IG in long-term mortality. We think that our study is the first study on this aspect.

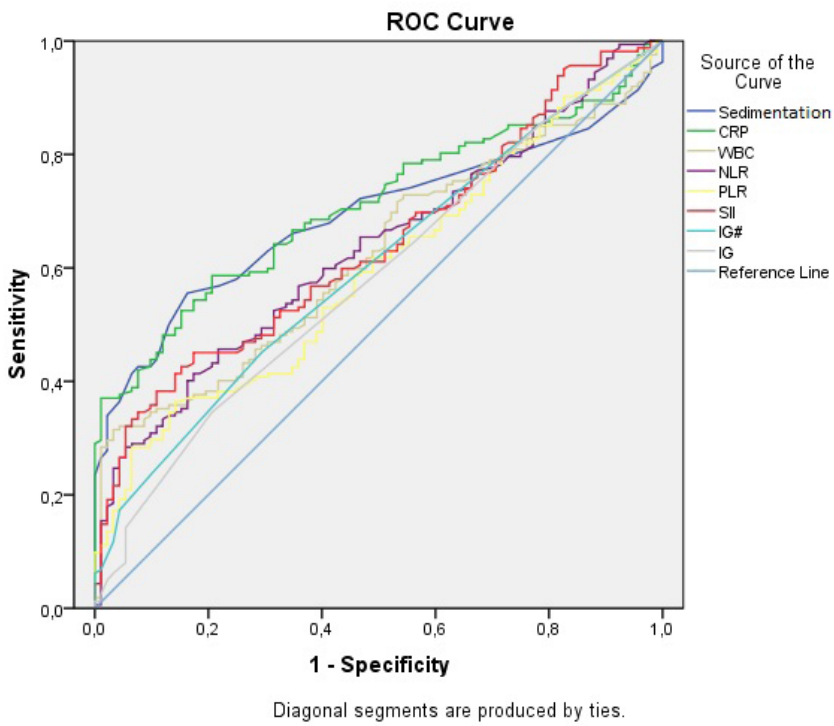

Figure 1. ROC curve analysis of some hematological data in short-term mortality in AIS patients

Table 6: ROC analysis values of some hematological and demographic data in evaluating long-term mortality in AIS patients

	Cut-off	AUC	95%CI	p	Sensivite%	Spesifite%
NLR	2.38	0.620	0.52-0.72	0.029	84	39
Age (Year)	83.5	0.764	0.68-0.85	<0.001	52	90
Length Of Stay	9.5	0.642	0.53-0.75	0.010	45	83
NIHSS	6.5	0.657	0.55-0.77	<0.001	39	88
RDV-CV%	13.75	0.644	0.55-0.74	0.09	61	65

Abbrevations: NLR, neutrophil-lymphocyte ratio; NIHSS, National Institutes Of Health Stroke Scale, RDW-CV, red blood cell distribution width – coefficient of variation

It has been proven that the inflammatory response plays an important role in the ischemic stroke process, and systemic inflammation increases the susceptibility to stroke. A chain of proinflammatory molecular and cellular occasions is induced at the onset of ischemia. Previous studies emphasize that the severity of this acute reaction is associated with clinical worsening, and cerebral damage. The relationship of stroke severity with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6, and tumor necrosis factor-α(TNF-α) has been shown in the literature. Studies have demonstrated that inflammation increases atherosclerosis and provides a link between atherosclerosis and atherothrombosis. After ischemic stroke, the permeability of the blood-brain barrier is impaired due to the migration of immune mediators and cytokines, resulting in cerebral edema, neuronal damage, and increased infarct volume.[8,9]

In current studies, it has been shown that many non-invasive markers are associated with poor diagnosis of AIS. In the latest studies, it's been shown that white blood cells have a role in early atherosclerotic conformation, which can result in AIS. Clinical studies have showed that early increased leukocyte and neutrophil counts are related to large infarct volumes and stroke severity. Furthermore, elevated neutrophil counts in patients with acute stroke are associated with a poorer 3-month outcome. Buck *et al*. observed that infarct volume and high NLR were related to

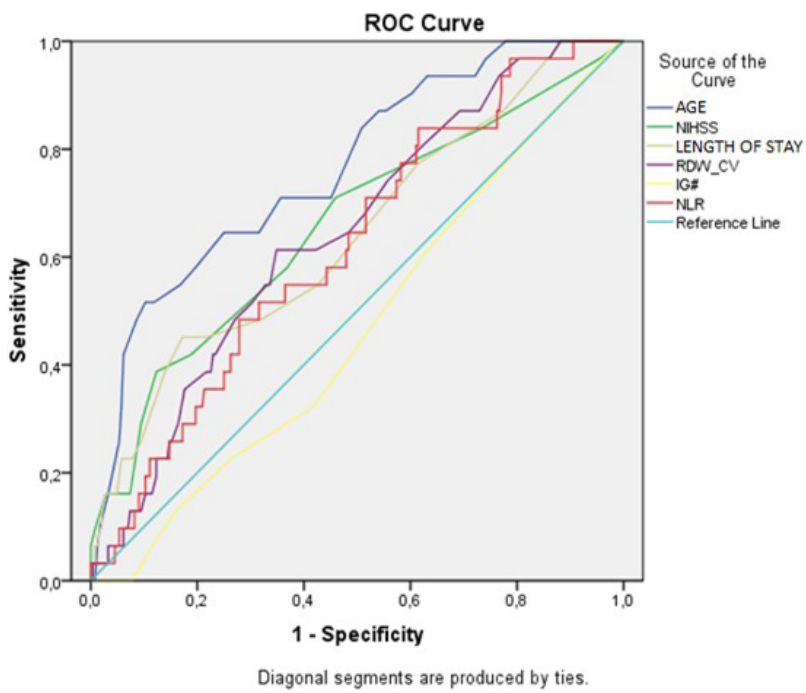

Figure 2. ROC curve analysis of some hematological data in long-term mortality in AIS patients

Table 7: Cox regression analysis of independent markers of short-term mortality in AIS patients

	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Gender	1.365(0.772-2.411)	0.284	1.828(0.912-3.662)	0.089
Age	1.019(0.988-1.051)	0.226	1,023(0.987-1.060)	0.217
DM	0.888(0.472-1.669)	0.712	1.637(0.759-3.528)	0.209
HT	0,723(0.381-1.375)	0.323	0.795(0.394-1.602)	0.521
NIHSS	1.102(1.053-1.154)	<0.001	1.107(1.055-1.161)	<0.001
IG%	1.508(1.150-1.978)	0.003	1.433(1.064-1.930)	0.018

Abbrevations: DM, diabetes mellitus; HT, hypertension; NIHSS, National Institutes Of Health Stroke Scale; IG%, immature granulocyte percentage

early mortality.[10,11] In our study, neutrophil counts and NLR were associated with poor prognosis and short-term mortality (Table 4). Martínez-Velilla *et al*. showed that erythrocyte distribution width (RDW) is associated with mortality in geriatric patients with AIS. In addition, it has been demonstrated that RDW is higher in patients who died due to a stroke.[12] Our study has shown that RDW-SD and RDW-CV were significantly elevated in the deceased group. In addition, our study also showed that mortality was significantly lower in patients using ASA compared to those not using ASA. In a meta-analysis, Raju *et al*. showed that ASA is a factor in reducing mortality.[13] This has been attributed to the antithrombotic and anti-inflammatory effects of ASA. In addition, studies have found that statins significantly reduce mortality in AIS.[14] In our study, mortality was also significantly lower in patients using statins. As in numerous studies, we determined a significant relationship between NIHSS at the time of first admission and short-term mortality in our study.[15,16] A critical relationship was observed between the length of hospitalization and short-term mortality, possibly due to hospital infections and other complications.

Various studies showed different results of long-term mortality in AIS. In Hankey's study, increasing age was the strongest predictor of death within 1-5 years after stroke.[17] Bryndziar *et al*., on the other hand, found that statin use, history of heart failure, age of stroke, and admission NIHSS score predicted 1-year mortality.[18] In a recent study, age, NIHSS, RDW, NLR, and eosinophils were independent prognostic factors in long-term mortality.[19] Quan *et al*., on the other hand, showed that NLR in the first 24 hours of stroke is associated with long-term outcomes.[20] In our study, similar to others in the literature, we found that increasing age was the most decisive parameter in predicting 14-month mortality (Table 5). In addition, length of stay, RDW, NLR, and PLR were significantly associated with long-term mortality. One of the striking results of our study was that the decreased percentage of eosinophils was associated with long-term mortality. The previous studies showed that increased stress response suppresses the rate of peripheral eosinophils. A reduced ratio of eosinophils would cause a more robust stress response, which might be related to the poor prognosis in AIS.[21] RDW was recognized as an inflammatory marker, which

Table 8: Logistic regression analysis of independent markers of long-term mortality in AIS patients

	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Gender	1.037(0.489-2.198)	0.924	0.547(0.230-1.304)	0.173
Age	0.899(0.857-0.944)	<0.001	0.894(0.848-0.943)	<0.001
DM	1.245(0.512-3.027)	0.629	1.118(0.410-3.048)	0.828
HT	1.206(0.543-2.675)	0.645	1.333(0.526-3.377)	0.544
NIHSS	0.823(0.740-0.915)	<0.001	0.816(0.723-0.922)	0.001
IG%	1.431(0.304-6.744)	0.650	1.375(0.324-5.841)	0.666

Abbrevations: DM, diabetes mellitus; HT, hypertension; NIHSS, National Institutes Of Health Stroke Scale; IG%, immature granulocyte percentage

was explained by its positive correlation with the well-known CRP and ESR markers (Table 4).

IG is a new inflammatory marker that can be rapidly measured from peripheral blood without an extra device. In recent years, with technological developments, several biomarkers, such as IG, have started to be used for diagnosis and prognostic purposes related to many diseases. IG is not typically detected in the peripheral blood of healthy individuals. However, it can be determined in the peripheral blood in inflammatory conditions.[32] Current research has shown that IG may be a biomarker of infection in the early stage of many sicknesses.[22] Studies have shown that elevated IG values are related to inflammatory illnesses such as acute appendicitis and pancreatitis and may contribute to the early diagnosis of these diseases. In addition, IGs may help predict the prognosis of these diseases.[23] Huang *et al*., in their study of cases with acute pancreatitis, showed that high IG values prognosticated the threat of developing early ARDS more effectively than known pancreatitis risk scores.[24] Bedel *et al*. found a correlation between mortality and high IG count in patients with acute coronary syndrome.[25] In addition, Korkut *et al*. found the mortality rates in ST-elevation myocardial infarction to be significantly higher in the high IG group compared to the low IG group.[7] Moreover, Korkut *et al*. found that high IG levels were significantly associated with 30-day mortality in AIS.[5] Our study showed a statistically significant correlation between high IG value and short-term mortality in cases with AIS. In univariate and multivariate Cox regression analyses, IG% was an independent predictor of short-term mortality. Univariate and multivariate logistic regression analyses showed that the number and percentage of IG were insignificant in demonstrating long-term mortality. However, we could not find any study on the long-term mortality of immature granulocyte in the literature.

This study has several limitations. It is a single-center, retrospective study. Second, the time from the onset of symptoms to the time of sampling has yet to be precisely determined. The clinicians can make serial IG measurements in further studies. Prospective multicenter studies are needed to exhibit that IG may be used as a prognostic marker in sufferers with AIS.

In conclusion, while IG, together with NIHSS and length of stay, shows moderate and high-level predictive properties in predicting short-term mortality in patients with AIS, it is ineffective in showing long-term mortality. Age is the most predictive predictor of long-term mortality in patients with AIS.

DISCLOSURE

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Conflicts of interest: None

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